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Evaluation of spinal cord injury animal models

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Abstract

Because there is no curative treatment for spinal cord injury, establishing an ideal animal model is important to identify injury mechanisms and develop therapies for individuals suffering from spinal cord injuries. In this article, we systematically review and analyze various kinds of animal models of spinal cord injury and assess their advantages and disadvantages for further studies.

Key Words: *nerve regeneration; spinal cord injury; animal model; establishment; evaluation; reviews; neural regeneration*

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Introduction

As the economic development all over the world, spinal cord injury (SCI) occurs with an annual incidence of 12.1–57.8 cases per million (van den Berg et al., 2010). Spinal cord injury is associated with permanent disability and decreased life expectancy (Hartkopp et al., 1997). It results in varying degrees of paralysis, sensory loss, and bladder/bowel dysfunction. The effects of SCI are not limited to an individual's health—it also creates an enormous financial burden for families and society at large (Pickelsimer et al., 2010).

In most developing countries, the majority of patients are young adults (20–40 years of age), thereby inflicting a high burden to these countries (Ackery et al., 2004). Traumatic SCI is more prevalent in males than females (Sekhon and Fehlings, 2001). Motor vehicle collisions (MVCs) and falls are the leading causes of SCI, and a trend toward an increased prevalence of falls and MVC in developing countries is likely related to urbanization and increased use of motor vehicles. Falls carrying a heavy load is another common cause of SCI in agricultural economy countries (Hoque et al., 1999). Sports-related SCI has also been discussed for diving athletes. Because there is no curative treatment for SCI, establishing an ideal animal model is important to develop therapies for individuals suffering from SCI. Over the past 30 years, there has been substantial worldwide research for establishing animal models, and a large number of therapeutic strategies have been developed (Kwon et al., 2011; Tetzlaff et al., 2011). In this article, we systematically review and analyze the literature about animal models of SCI, and assess their advantages and disadvantages for future studies on SCI.

Experimental animals

The pathology of human SCI is not greatly different from that of experimental animals, although important specific differences exist. Like contusion injury in humans, rat contusion injury leads to the formation of both small and large cavities and fluid-filled cysts (Sroga et al., 2003; Norenberg et al., 2004). A similar contusion injury in mice results in the development of a dense connective tissue matrix that more closely resembles the long-term effects of some laceration and massive compression injuries in humans (Sroga et al., 2003; Norenberg et al., 2004). Over the last 10 years, numerous animals have been used for studying SCI, mainly including rats, mice, dogs, rabbits, pigs, and nonhuman primates (**Table 1**).

Some studies have predominately used rodents for *in vivo* SCI modeling and experimentation (Gonzalez-Lara et al., 2009; Basoglu et al., 2013). These studies have brought to light the pathophysiology of SCI and a growing number of novel treatments that promote behavioral recovery. There are numerous advantages of using rodents as models of SCI (Blight, 1992). For example, some animal studies benefit from the treatment of acute SCI. However, clinical trials have, thus far, been uniformly disappointing. There are some discrepancies between the promising animal studies and clinical trials, as well as the potential barriers in the translation of results from animal studies to humans (Akhtar et al., 2008). Methods for reproducible and controlled SCI models have been well described. These include contusion impactors (Krishna et al., 2013) and clip compression (Alluin et al., 2011). In addition, a multitude of behavioral outcome measures have become widely available. These include the Basso, Beattie, Bresnahan (BBB), the locomotor scale (Zeman et al., 2008), the cylinder rearing test (Lee et al., 2010), the horizontal ladder test (Lee et al., 2010), and the catwalk (Van Meeteren et al., 2003). These endpoint measurements produce interpretable and comparable results between studies. Histological, biochemical, and molecular techniques for

Table 1 Spinal cord injury animal models used in the past 10 years

	Experimental animal							
	Rat	Mouse	Dog	Rabbit	Pig	Primate	Guinea pig	Total
Number of articles	289	69	19	18	9	2	1	407

Table 2 Comparison of different methods used for spinal cord injury (SCI)

Model	Animal	Methods	Characteristics
Ischemia/reperfusion injury model	Rat, mouse, swine, rabbit	Aortic cross-clamping; aortic occlusion	Suitable for spinal cord ischemia caused by thoracic or thoracoabdominal aortic aneurysm surgery with some complications
Traumatic injury model	Rat, dog	Allen's method (Koozekanani et al., 1976)	Classical, but lack of standardization of this injury model
	Rat	Modified NYU device	Standardized and expensive
	Rat, guinea pigs	Compressive injury model	Moderate chronic injury model for recovery or secondary dysfunction, and inflammatory response at the injury site
	Rat, mouse, pig	Tractive SCI model induced by a spinal distractor (Wang et al., 2011)	Cost-effective and reliable animal model
Completely transected	Rat, cat, mouse	Surgical incision	Acute model and low animal survival rate
Others	Rat	Photochemically induced, inflammatory injury model	Suitable for post-traumatic syringomyelia but not be widely used

assessing the outcome of SCI and/or its treatment have been well established. Furthermore, such small animal models are relatively inexpensive and require basic housing facilities readily available to most researchers. Despite these well recognized advantages, the SCI research community has also acknowledged the frustrating reality that even after the studies from these rodent models, clinical trials have failed to demonstrate convincing efficacy (Tator, 2006). Possible explanations for the discrepancy may be due to the heterogeneity of human SCI and the challenging nature of measuring neurological function in clinical trial settings (Kwon et al., 2011). However, at a more fundamental level, the differences in size, anatomy, and the pathophysiological responses to injury may quite possibly exist between SCI in rodents and in human patients. However, the direct translation of the results from rodents to clinical cases is difficult because of neurofunctional and anatomic differences between the two species. Prior to embarking on lengthy and expensive clinical trials, an animal SCI model that is an intermediary between both a rodent and human SCI may be a valuable translational research resource for pre-clinically evaluating novel therapies (Nout et al., 2012; Zurita et al., 2012; Lee et al., 2013).

Establishment of SCI models

For SCI research, it is essential to establish an ideal animal model of SCI. Ideal models should meet the following conditions (Akhtar et al., 2008): (1) simulate damage that is similar to clinical SCI; (2) be controlled, reproducible, and stable; (3) involve a simple technique that is easy to study; (4) the equipment used to make a model is straightforward and quick to produce.

Anatomical location

Differences in injury exist between experimental and clinical SCI. In both experimental and clinical SCI, contusion and compression are two of the most common injury types. However, in experimental animals, these injuries are most frequently induced dorsally and in the thoracic spine, whereas most clinical injuries occur anteriorly and in the cervical region (Akhtar et al., 2008). According to the National Spinal Cord Injury Statistical Center, in 2005, 51% of SCI cases in the U.S. occurred in the cervical region (Akhtar et al., 2008). Most SCI in humans affects the anterior spinal artery that supplies three quarters of cord tissue, in contrast to the dorsal arteries that are more commonly affected in experimental SCI (de la Torre, 1981).

Functional outcomes and assessment scales

Functional outcomes commonly used in experimental animal SCI include histopathological and electrophysiological measures, spinal cord blood flow, the Basso Mouse scale (Yu et al., 2014), and measurement of biomarkers such as lipid peroxidation. Evoked field potentials are commonly used to assess sensory and motor function in animals, however they mostly reflect the activity of large fibers and thus only a small part of axonal grouping is at the lesion site (Blight, 1992). Most methods of recording evoked potentials involve craniotomy and laminectomy for electrode placement, which allow for only single acute measurements (Sun et al., 2000). This lack of consistent correlation with functional outcome is another significant drawback with the use of surrogate markers. A great effort has been made to develop assessment scales and procedures to appropriately measure functional outcomes. Some of the most commonly used scales are the

BBB scale (Basso et al., 1995), the Tarlov open field test (Tarlov and Klinger, 1954), and the inclined plane test (Rivlin and Tator, 1977). Both the Tarlov and inclined plane tests assess general locomotor ability and do not reflect specific changes in motor or sensory function (Kunkel-Bagden et al., 1993). Although the BBB scale is an improvement from the Tarlov scale, it is far from a comprehensive evaluation of motor function. This scale assesses hindlimb function only, and does not assess other movements which require coordinated spinal cord activity (Akhtar et al., 2008). Motor and sensory dysfunction has been periodically assessed using open field locomotion scoring, thermal/tactile pain/escape thresholds, and myogenic motor evoked potentials. Gait (CatWalk) and ladder climbing have also been assessed (van Gorp et al., 2013). Overall, we can conclude that accurate measurement of fine motor and sensory function in animals, especially in rodents, is quite difficult. Treatment effectiveness in animals with SCI is often measured simply by whether or not independent ambulation has occurred.

Animal models of SCI

There are numerous experimental animal models of SCI, including the spinal cord ischemia-reperfusion injury model (Lafci et al., 2013), spinal cord traumatic injury model (Koozekanani et al., 1976), photochemical-induced SCI model (Piao et al., 2009), spinal cord transection model (Min et al., 2011), and bidirectional distraction SCI model (Seifert et al., 2011). However, SCI caused by impact and compression is more common in clinical patients. Some models are used for investigating pathophysiological mechanisms (**Table 2**) and others for investigating the mechanisms underlying tissue engineering and spinal cord regeneration (**Table 2**).

Traumatic SCI model

In 1911, Allen first created SCI models using a weight drop to affect the animal dorsal spinal cord, and this technique was later considered as a standard experimental spinal cord contusion injury model (Koozekanani et al., 1976). This method of inducing SCI may yield markedly different degrees of cord compression depending on the materials and apparatus. Some approaches to the standardization of this injury model have been suggested (Yeo et al., 2004). Experimental SCI is induced by dropping calibrated weights through a vented tube onto a small impounder resting on the surgically exposed cord (Koozekanani et al., 1976).

Contusive SCI models: To establish an experimental animal model of contusive SCI, a pneumatic impact device was made in Korea to induce a contusive injury on the dorsal spinal cord (Yeo et al., 2004). A NYU MASCIS (New York University, Multicenter Animal Spinal Cord Injury Study) impactor and an Ohio State University electromagnetic spinal cord injury device have been used to induce SCI in rodents, but these impact devices are expensive. A cost-effective approach for an experimental SCI rat model has been to create a customized impact device (Vijayaprakash and Sridharan, 2013), which is a customized blunt-force impact device designed to induce a standard animal model of contusive SCI at the thoracic level.

Compressive SCI model: A model of spinal cord trauma in guinea pigs is based on the concept of compression to a set thickness as an alternative to compression or contusion with a set force or displacement. This model is technically simple and reliable, and it was designed initially to produce moderate injuries, allowing significant recovery of function (Blight, 1991). Recently, some studies have adopted some experimental devices, designed in-house, to construct standardized ventral and dorsal rat SCI models (Zheng et al., 2012). They have used different weights falling from varied heights, leading to transversal compression on the spinal cord. To induce SCI, a 35-g circular rod is placed on the exposed L3 spinal segment and the spinal cord is compressed in the dorso-ventral direction for 15 minutes. This results in gradual increases in the degree of histopathological injury leading to decreased Tarlov and BBB scores for the behavioral test and increased Ashworth scores for the hind limb. Similar alterations have been observed in the ventral SCI rats proportional to the increase in compression weight (Zheng et al., 2012). These experimental findings indicate that the standardized experimental rat models of dorsal and ventral SCI may be stable, reliable, and reproducible.

Tractive SCI model: To establish an animal model of tractive SCI in rats, Liu et al. (2004) used spines that were tracted longitudinally with a special spinal retractor that was put on the processus transversus vertebrae of the rat after exposing the spinal cord to dual laminectomy. The tractive SCI rat models can also be successfully established with a spinal impactor, and monitoring the somatosensory evoked potential for several minutes is more suitable for studying tractive SCI (Wang et al., 2011). The tractive SCI model is a reliable animal model for studying pathological mechanisms and treatment of tractive SCI (Wang et al., 2011).

Complete SCI model: In some studies, a surgical incision has been used to sever the spinal cord to establish completely transected SCI models. The majority of studies for the recovery of locomotion from SCI have used rats (65%) and the remainder have used cats (23%) or mice (12%). The level of SCI in completely transected animals has ranged from T6 to T13 with 47% between T9 and T11 (Battistuzzo et al., 2012). Implantation of scaffolding biomaterials is applicable to this kind of SCI model, and these biomaterials provide effective bridging and stimulating effects on neural regeneration and prevent the formation of glial scars in the completely transected SCI rat models (Han et al., 2010).

Ischemia-reperfusion SCI injury model

Spinal blood flow plays a significant role in maintaining spinal function. Thoracic or thoracoabdominal aortic aneurysm surgery may cause spinal cord ischemia. Such animal models have been established *via* transient aortic occlusion by cross-clamping the descending aorta through a lateral thoracotomy (Awad et al., 2010). Lee et al. (2008) investigated whether ischemic tolerance could be induced by ischemic preconditioning of the spinal cord in a swine

model. Furthermore, ischemia/reperfusion injury may directly or indirectly be responsible for aortic cross-clamping, and may result in severe postoperative complications caused by SCI (Lafci et al., 2013). Lozos et al. (2013) have reported that Aprikalim reduces the severity of ischemic SCI by 30 minutes of normothermic aortic cross-clamping in a rabbit model of spinal cord ischemia (Lozos et al., 2013). To accurately evaluate ischemic injury of the spinal cord, endoprosthesis implantation in the thoraco-abdominal aorta has been used (Vaquero et al., 2007).

Inflammatory SCI model

Inflammation is known to be detrimental to the neurologic outcome during the acute phase after an injury, and therefore provides a potential target for preventive or therapeutic approaches for spinal cord ischemia-reperfusion injury (Li et al., 2014). Spinal cord ischemia has been induced by balloon occlusion of the thoracic aorta in Sprague-Dawley rats (Fan et al., 2011).

Photochemical-induced SCI model

With the exposed spinal column intact, 560 nm light irradiation of the dorsal surface induces excitation of the systemically injected dye, rose bengal, in the spinal cord microvasculature (Watson et al., 1986). The resultant photochemical reaction leads to vascular stasis, and voluntary motor function is consistently lost in the subacute phase of injury (Watson et al., 1986). Hao et al. (1991) developed a rat model of photochemical-induced SCI, in which female rats were intravenously injected with Erythrosin B and the T_{10} vertebra was irradiated with a laser beam for 1, 5 or 10 minutes. These procedures initiated an intravascular photochemical reaction, resulting in ischemic SCI. Vascular thrombosis, resulting from an intravascular photochemical reaction induced by a rose Bengal-laser beam interaction, led to an extensive area of tissue deterioration, termed the "lesion cavity" within a few days (Bunge et al., 1994). This model technique may provide an appropriate milieu to better understand the aspects of the vexing problem of post-traumatic syringomyelia in the human.

Conclusions and perspectives

SCI animal models, including the contusive, compressive, tractive, photochemical-induced, inflammatory injury, and ischemia-reperfusion injury models have been mostly used for investigating the pathophysiology of SCI. However, the completely transected SCI models have been usually used for tissue engineering and spinal cord regeneration.

Several major problems still exist in understanding SCI in animal models and humans: (1) the lack of anatomical and pathophysiological correlation between experimental SCI and clinical SCI; (2) lack of congruent SCI pathology between different species and strains; (3) difficulties in interpreting outcomes measured in animals.

In the future, several points should be addressed. Species and strains of SCI need to be standardized. In these studies, environmental conditions may diminish some of the difficulties involved in performing and interpreting behavioral tests, and thus may serve to improve comparisons between studies. Standardizing laboratory procedures for different species and strains may also decrease the differences between normal and injured spinal cord biochemistry. However, there have been few such relatively direct studies.

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